NTP
National Toxicology Program

Research Concept for Butterbur

Paul C. Howard, Ph.D.
National Center for Toxicological
Research, Food and Drug Administration

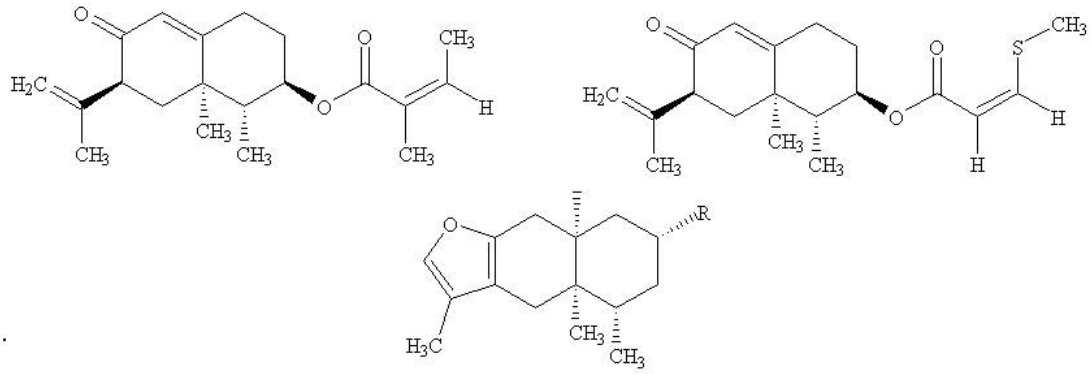
NTP Board of Scientific Counselors
9-10 December 2009

Background/use

- Source: traditionally *Petasites hybridus*; underground rhizomes, large rhubarb-like leaves; temperate zone in wet soils, damp woods, river ba America, Europe, Asia
- Ancient use: herbal remedy for pain, headaches, fever, skin ulcers, urogenital (dysmenorrhea) and digestive spasms, emmenagogue, coughs.
- Modern use: migraines & tension headache, urogenital and gastrointestinal spasms, asthma, allergic rhinitis, gastric ulcers, pain relief, chronic cough (including whooping cough), chills, anxiety, plague, fever, insomnia, wounds, anti-inflammatory.
- Multiple potential sources: *e.g. Petasites formosanus* Kitamura
- Available forms: capsule, extract, powder, tincture, softgel.

Background/composition

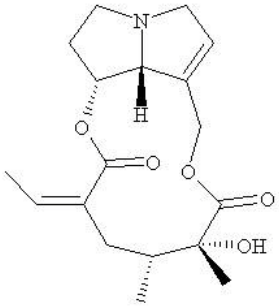
- Complex mixtures: carbon-dioxide extracts contain sesquiterpenes, fatty acids, aromatics, phytosterols, and unknown compounds
- Sesquiterpenes include petasin and S-petasin (iso- and neo-isomers), and furanopetasin:



- Butterbur extracts: "standardized" to have at least 7.5 mg petasin and isopetasin per 50 mg extract (15 wgt-%); one stated dose is 4.5-7 g extract/day (68-105 mg petasin + isopetasin)

Background/composition

- *Petasites hybridus* (leaves, rhizomes, etc.) contain hepatotoxic pyrrolizidine alkaloids such as senecionine and integrrimine.



- Manufacturers claim to eliminate the pyrrolizidine alkaloids using extraction methods.

Toxicology/rodent

- Acute
  LD_{50} established in Wistar rats (oral, ≥2,500 mg/kg; *i.p.*, ≥1,000 mg/kg)
- Subchronic
  No data available.
- Reproductive/developmental
  No data available
- Chronic
  26-week oral study with Wistar rats – incomplete
- Initiation/promotion
  No data available
- Genotoxicity
  Mutagenic in TA98 and TA100.

Toxicology/rodent

In vitro

- Extracts inhibited histamine and leukotriene induced contractions in guinea pig trachea strips; Ca^{++} channel blocker.
- Extracts inhibited hexosaminidase release, leukotriene synthesis, and THFa production in sensitized mast cells.
- Petasin inhibited LPS-induced PEG2 release and MAPK activation in microglial cells.

In vivo

- S-petasin modulates endocrine metabolism in rat testicular cells and Leydig cells; *in vivo* and *in vitro*, inhibits testosterone release
- S-petasin decreased heart rate, right atrial firing rate, inhibited left atrium, affected L-type Ca^{++} channels.
- Vasorelaxation effect on vascular smooth muscle cells.

Toxicology/human

- Clinical studies on Butterbur
  - Some effectiveness against allergic rhinitis and treatment of migraines
  - Questionable effectiveness against asthma and allergic skin disease
  - Adverse side effects of Butterbur use (listed in Background document).
- Epidemiological studies (none).
- Butterbur not recommended for persons who:
  - Pregnant or nursing.
  - Allergies to *Petasites* species.
  - Using anticoagulants, barbiturates, or anti-hyperglycemics
  - Liver disease

Nomination and Proposed Testing

- Butterbur was nominated for toxicology studies by NIEHS
- Rationale:
  - Widespread use (dietary supplement; claims of clinical effectiveness).
  - Some constituents are toxic
  - General lack of robust toxicity data for risk assessment
- Proposed tiered toxicity program:
  - Establish consensus Butterbur preparation
  - *In vitro* screening
  - Subchronic toxicity
  - Reproductive/developmental toxicity
  - Carcinogenicity (chronic toxicity)

Test article (consensus preparation)

- **Butterbur preparation**
  - FDA and NIEHS collaboration; determine the range of *Petasites* species used in modern Butterbur preparations.
  - Establish extracts of representative preparations.
- **Pyrrolizidine alkaloids**
  - The FDA position is that any preparation containing pyrrolizidine alkaloids may be adulterated and therefore may be inappropriate for marketing (confirm levels in consensus preparation).

Acute and Subchronic Studies

- ***In Vitro* Screening**
  - Chemical characterization of marketed preparations.
  - Evaluate activity/toxicity of preparations on market.
  - Used to select consensus preparation.
- **Repeated dose toxicity studies (28-day)**
  - Standard toxicity endpoints in rats and mice (especially cardio-, neuro-, and hepato-toxicity).
- **Developmental/Reproductive toxicity**
  - Conduct pre- and peri-natal exposure in rats (oral route).

Reproductive/developmental and chronic toxicity studies

- **Subchronic Toxicity (90-day)**
  - Rats and mice, oral route
  - Special study rats for serum hormone levels
  - Standard toxicity endpoints (especially cardio-, neuro-, hepato-toxicity)
- **Carcinogenesis (2-year)**
  - Rats and mice; oral route

Significance of Proposed Research Program

- Provides toxicological data to enable:

  (i) quantification of toxicity of Butterbur and constituents;

  (ii) generation of data for developing risk assessment of Butterbur dietary supplements and herbal preparations.